REMARKS

Claims 49-50, 63-71, 77-81, 83, 88, 89, 91 and 92 are pending in the present application. Claims 83, 88, 89 and 92 have been withdrawn from consideration. Claim 49 has been amended so as to delete "solvate". Claim 80 has been amended so as to include the entire proper phrase "selected from the group consisting of".

Removal of Issue under 35 USC 112

Claims 49, 50 63-71, 77-81 and 91 have been rejected under 35 USC 112, first paragraph, because of the term "solvate". This term has been removed from claim 49, such that the basis for this rejection has been removed. It is requested that this rejection now be withdrawn.

Issues under 35 USC 103(a)

Claims 49, 63-65, 67, 69-71, 77, 78, 81 and 91 have been rejected under 35 USC 103(a) as being unpatentable over Ottosen '744 (WO 2001/05744) in view of Revesz '447 (WO 2002/76447). This rejection is traversed based on the following reasons.

Patentable Distinctions over Ottosen '744 and Revesz '447

In support of the above obviousness rejection, the Examiner has again identified Example 9, Compound 118 of Ottosen '744. The Office Action includes a compound structure at the bottom of page 4 with the assertion that Ottosen '744 discloses this compound as Example 9. This is simply incorrect. This structure at the bottom of page 4 of the Office Action incorrectly shows a ***nitro*** group bonded to "Ring C" which is the end phenyl ring bonded to the carbonyl linking group (not bonded to the amino linking group). However, the compounds of Ottosen '744 require an ***amino*** group (not a nitro group as shown in the Office Action) attached to the Ring C phenyl ring. In formula II of Ottosen '744, the nitrogen-atom of Ring C may be substituted with hydrogen, CF_3, alkyl, carbamoyl, alkoxycarbonyl or alkaloyl. The R_3-group can not be nitro.

The present claims differ in scope significantly from the compounds disclosed by Ottosen '744. First, the claimed compounds do not include an amino group as a possible R_3 or R_4 substituent in formula I in the present claims. Rather, R_3 and R_4 in the claimed compounds are

both fluoro in fixed positions on Ring C. Therefore, significant structural distinctions exist over the compounds of Ottosen '744.

Revesz '447 discloses compounds of formula I wherein R4 in Ring C may be 1-3 halogens, and the middle phenyl ring ("Ring B") is unsubstituted. The Examiner refers to Example 3 on page 14 which shows a structure with fluoro atoms at the para and meta positions on Ring C (with respect to the linking amino group) and an unsubstituted middle Ring B. Revesz '447 fails to disclose or suggest the compounds of formula I of the present claims, wherein Ring B must be substituted. Therefore, significant structural distinctions exist over the compounds of Revesz '447.

Asserting that Ottosen '744 is the closest prior art, the Examiner acknowledges that Ottosen '744 fails to disclose any compounds wherein R3 and R4 are fluoro, with R3 being meta to R4 and para to the linking amino group. The Examiner further acknowledges novelty over Revesz '447 but concludes that since Revesz '447 discloses the above-noted Example 3 compound, "...it would have been obvious to one of ordinary skill in the art..... to synthesize the compound of Ottosen et al. and modify the R3 and R4 groups with the fluorine atoms of Revesz with a reasonable expectation of success."

Applicant respectfully disagrees. First of all, one skilled in the art would not be motivated to replace the optionally substituted amino group in Ring C of the compounds of Ottosen '744 with a fluorine atom, since the optionally substituted amino group in Ring C of Ottosen '744 constitutes an essential part of the structure of the compounds disclosed therein. Secondly, one skilled in the art would find no reasonable basis for a motivation to place a substituent on the middle Ring B of the compounds of Revesz '447. Essentially, the Examiner is arguing that one skilled in the art would be motivated to make two significant structural changes, one in each of the compound sets of Ottosen '744 and Revesz '447, despite the fact that all compounds in both references do not have these structural features and both references fail to provide any suggestion or hint to make such modifications. Why would one skilled in the art decide to make both of these selective structural changes to the compounds of both Ottosen '744 and Revesz '447? This question remains unanswered apart from an unsupported conclusion that it would have been obvious.

If one skilled in the art studied Revesz '447 and were hypothetically inclined to try replacing an amino group on Ring C of an aminobenzophenone structure, he would learn from US 6,541,670 (Ottosen '670), which concern aminobenzophenone compounds similar to the present invention, that substitution on Ring C with fluoro would indeed ***not*** provide compounds with an improved TNF-α or IL-1β inhibitory activity compared to the similar compounds without the fluoro atom being present. In this regard, note that compounds 102, 116, 130, 131 in Ottosen '670 are identical except that compounds 116, 130 and 131 have a fluoro atom in the 4, 5 and 3 position, respectively, whereas compound 102 has a hydrogen atom in this position. The skilled person comparing these compounds would find that compounds 116 and 130 indeed show a difference in the pharmacological properties compared to compound 102, but in a non-beneficial way. In fact the TNF-α or IL-1β inhibitory activity for 116 and 130 are considerably decreased compared to compound 106 and at the same level for compounds 131 and 102. See IC_{50}-values (nM) extracted from table 1 in Ottosen '670 below:

Compound:	IL-1β	TNF-α
102	13	4.0
116	2	7.9
130	40	6.3
131	13	4.0

For comparison, the compounds of the present invention show IL-1β and TNF-α inhibition concentration-values (IC_{50}) of <13 nM and <4 respectively as evidenced by the results in Table 1 in the present application as filed.

Therefore, a skilled person having reviewed Revesz '447 and Ottosen '670 would indeed not be able to predict that replacing an optionally substituted amino group in the C-ring in a benzoaminophenone compound similar to the compounds according to the present invention would yield compounds with a considerably improved inhibitory TNF-α or IL-1β activity. Further, one skilled in the art would not have any reasonable basis to be inclined to replace the

optionally substituted amino group in Ring C with two fluoro groups, as the optionally substituted amino group constitutes an essential part of the structure of the compounds disclosed in Ottosen '744. Consequently, significant patentable distinctions exist over both Ottosen '744 and Revesz '447, whether taken separately or improperly combined.

Further in addition to the above, one skilled in the art, with knowledge of Revesz '447 and Ottosen '670, would indeed not be able to predict that replacing a hydrogen atom in Ring C in a benzoaminophenone analogue of compounds according to the present invention and adding a substituent at the 3 position of middle Ring B, would yield compounds with a considerably improved inhibitory TNF-α or IL-1β activity compared to the benzoaminophenone analogues described in the prior art. Revesz '447 does not disclose any *in vitro* inhibition data, but reports that agents of the invention typically inhibit *in vivo* TNF-α production from about 50% up to about 90% or more when administered at 30 mg/kg p.o. (page 42). As can be seen from Table 3 of the present application, compounds of the present invention inhibit *in vivo* TNF-α production from about 44% to 99% when administered at just 1 mg/kg p.o. Thus, the dosing of compounds of the present invention is 30 times less in comparison to the dosing of the compounds of Revesz '447 in an otherwise comparable assay. Compounds of the present invention therefore show unexpected, advantageously improved biological activity *in vivo* with respect to inhibition of LPS induced TNF-α production in mice compared to the compounds of Revesz '447, with no recognition of this improvement mentioned in either the Revesz '447 or Ottosen '744 references.

In conclusion, it is the position of the Examiner that it would have been obvious to replace the optionally substituted amino group on Ring C of the compounds of Ottosen '744 with two fluoro groups (at the meta and para positions), or to place a substituent on the middle Ring B of Revesz '447 even though none exists in any of the disclosed compounds, or to selectively combine structural features of both sets of compounds from each reference, in an attempt to obtain the presently claimed compounds. However, the present record is not only devoid of any reasonable basis to suggest any improvements with such modifications, but the most relevant evidence noted above suggests that such modifications would provide inferior results. In this regard, note that there must be some evidence of at least a reasonable expectation of success to support such modifications. *KSR International Co. v. Teleflex Inc.*, 85 USPQ2d 1385, 1395 (US

Sup. Ct. 2007). The only basis for selectively combining Ottosen '744 with Revesz '447 is improper "hindsight reconstruction" which ignores the fact that both references disclose compound structures inconsistent with the proposed modifications and suggesting to one skilled in the art that such modifications would render the compounds unsatisfactory for their intended purpose. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Consequently, the above rejection fails to be supported and must be withdrawn.

Double Patenting Rejection

Claims 49, 50 63-71, 77-81 and 91 have been rejected on the ground of obviousness-type double patenting as being upatentable over claim 1 of Revesz '447 (WO 2002/76447). This rejection is traversed based on the following reasons.

The above rejection is improper, since any "double patenting" rejection must be based on a claim of a granted U.S. patent, or must be provisionally based on a claim of a co-pending U.S. patent application. The cited Revesz '447 document is not a U.S. patent or a co-pending U.S. patent application. Further, any double patenting rejection must be based on a granted U.S. patent or co-pending U.S. patent application that has the same owner as the rejected application. This also does not appear to true. Therefore, it is requested that this rejection be withdrawn.

It is submitted for the reasons above that the present claims define patentable subject matter such that this application should now be placed in condition for allowance.

If any questions arise in the above matters, please contact Applicant's representative, Andrew D. Meikle (Reg. No. 32,868), in the Washington Metropolitan Area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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